

HOT-MELT TTS FOR ADMINISTERING ROTIGOTINE

[0001] **This application claims the benefit of U.S. provisional application Serial No. 60/453,498 filed on March 11, 2003, and of German application No. DE 102 34 673 filed on July 30, 2002.**

FIELD OF THE INVENTION

[0002] This invention relates to a transdermal therapeutic system (TTS) encompassing a **Rotigotine rotigotine**-containing cement matrix, characterized in that the cement matrix contains a hot-melttable adhesive in which the active substance **Rotigotine ~~((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl)-amino]-1-naphthol]~~ rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl)-amino]-1-naphthol])** is dispersed and partly or completely dissolved.

[0003] The invention further relates to a method for producing a TTS that encompasses a cement matrix containing **Rotigotine rotigotine** as the active substance, characterized in that, prior to the coating and laminating, the components of the cement matrix are melted and homogenized, without any solvent, at temperatures between 70 and 200°C[.] and preferably between 120 and 160°C.

[0004] Finally, this patent application relates to the use of **Rotigotine rotigotine** for producing the cement matrix of a TTS by the hot-melting process.

BACKGROUND

[0005] Prior art has described various TTSs for the administration of **Rotigotine rotigotine**.

[0006] WO ~~94-07468~~ **94/07468** discloses a system that contains as the active substance a salt in a diphasic matrix.

[0007] That diphasic matrix consists of a hydrophobic polymer in which a silicate is dispersed to accept the hydrophilic medicinal salt, assisted by the additional use of organic solvents. The matrix is produced by drying the dispersion at 70°C. The **Rotigotine rotigotine** content in the matrix is 2–5% by weight.

[0008] That system, however, has a number of drawbacks:

- (1) Its production is a multi-stage, complex process. The active substance must be dissolved in water or in an aqueous solvent mixture, then mixed with the silicate,

SUBSTITUTE SPECIFICATION (MARK-UP)

then mixed with an emulsifier so as to finally emulsify the aqueous solution with the polymer such as a silicone cement dissolved in an organic solvent, typically heptane, ethyl acetate or toluene. The resulting emulsion is difficult to manipulate.

- (2) Organic solvents are used which, during the TTS production, have to be completely removed again so as to ensure an adequate shelf life as well as reproducible release characteristics of the TTS while preventing skin irritations. That increases the production cost. Up to the point where the cement contains the active substance, it is a discontinuous process.
- (3) Handling organic solvents requires stepped-up safety precautions to prevent any environmental impact or exposure of the personnel involved in the TTS production. Solvent recovery/separation equipment, measures for personnel protection and the disposal of solvents are all costly.
- (4) On the one hand, the admixture of the active substance is limited by the degree of solubility of the **Rotigotine** rotigotine in the solvent concerned. On the other hand, as the solvent is removed during the production process, the relative concentration of the active substance increases, which can lead to an oversaturation of the matrix and to an undesirable formation of crystals. This again places a limit on the maximum amount of the active substance that can be worked into the matrix. Yet a low-level infusion of the active substance limits the release capacity of the matrix per unit of time and/or its functional lifespan due to a premature depletion of the active substance.
- (5) The thickness of the matrix that can be obtained in one production step is limited to about 100 μm (equaling about 100 g/m^2) if it is to ensure the complete removal, in the drying process, of the solvent needed for its production. If cement matrices with a thickness greater than about 100 μm are required, they must be built up layer by layer, which is a complex and cost-increasing operation.
- (6) The silicate or **silicone** silicon oxide remaining in the adhesive patch constitutes a diffusion barrier for the active substance and may negatively affect the release of the latter. It also affects the water absorption of the adhesive patch. The formation of pores by the removal of water-soluble matrix components at the interface with the skin can lead to an insufficiently controllable release of the active substance.

SUBSTITUTE SPECIFICATION (MARK-UP)

[0009] WO 99/49852 describes a TTS with **Rotigotine rotigotine** in its free-base form containing an acrylate- or silicone-based adhesive system. For producing either system, solvents are again used that will later have to be removed again, involving the same drawbacks and limitations described under (2) to (5) above.

[0010] In terms of the infusion and release of **Rotigotine rotigotine**, the two matrices described in WO 99/49852 have these additional shortcomings:

[0011] Silicone matrices: Assuming an emulsion or solution containing an active substance, the matrix can accept **Rotigotine rotigotine** at about 15% by weight. In other words, there are limits to the admixability of active substances in silicone matrices. Increasing the **Rotigotine rotigotine** admixture for instance in the production of multi-day patches is possible only by adding more matrix layers, which, however, requires several procedural steps that make the production more complex and expensive.

[0012] Acrylate matrices: By means of solvent coating, acrylate matrices can accept **Rotigotine rotigotine** at up to about 40% by weight. However, the higher absorption capacity of these matrices for **Rotigotine rotigotine** is offset by a reduced capacity to release it onto the skin due to an agent-distribution coefficient that is inferior to that of silicone systems. Obtaining adequate **Rotigotine rotigotine** plasma levels from these systems requires very high charge rates. Yet relatively large amounts of the active substance remain in the patch after its use, increasing the effective cost of these systems while being undesirable from the perspective of drug safety.

[0013] It is therefore the objective of this invention to provide a TTS that avoids the drawbacks and limitations associated with the use of solvents. In particular, the **Rotigotine rotigotine** TTS should offer the highest possible degree of flexibility in admixing **Rotigotine rotigotine** even in larger amounts while releasing the **Rotigotine rotigotine** in therapeutically effective quantities.

[0014] The problems described above have been solved by providing, as the first of its kind, a TTS with a **Rotigotine rotigotine**-containing cement matrix, characterized in that the cement matrix is produced in a hot-melting process, whereby the cement matrix contains a hot-melttable adhesive in which **Rotigotine rotigotine** as the active substance ((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl)-amino]-1-naphthol) ((-)-5,6,7,8-tetrahydro-6-

SUBSTITUTE SPECIFICATION (MARK-UP)

[propyl][2-(2-thienyl)ethyl-]amino]-1-naphthol) is dispersed and partly or completely dissolved.

ILLUSTRATIONS BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIGS. 1a and b show comparisons of **Rotigotine** rotigotine permeation through murine skin (HMS), between a hot-melt silicone TTS and a solvent-based silicone TTS. FIG. 1a illustrates the release from either TTS each with a **Rotigotine** rotigotine content of 9% by weight. FIG. 1b shows the effect of a higher **Rotigotine** rotigotine charge on the **Rotigotine** rotigotine permeation from the hot-melt TTS through the murine skin.

[0016] FIG. 2 shows the effect of the wax content on the permeation through murine skin of **Rotigotine** rotigotine from the hot-melt silicone TTS with a constant 9 weight[[-]] % charge of the active substance.

[0017] FIGS. 3a and b show the effect of the **Rotigotine** rotigotine charge on the **Rotigotine** rotigotine permeation through murine skin from the silicone-based hot-melt TTS in the presence of 15% wax (3a) and, respectively, 5% wax (3b).

[0018] FIG. 4 illustrates the effect of the matrix weight on the **Rotigotine** rotigotine permeation through murine skin from a silicone-based hot-melt TTS.

[0019] FIGS. 5a and b show the effect of the content of the internal-phase component on the cumulative (5a) and linear (5b) permeation of **Rotigotine** rotigotine from the hot-melt TTS through murine skin.

[0020] FIG. 6a shows the cumulative 72-hour permeation of **Rotigotine** rotigotine from a hot-melt silicone TTS through human skin in comparison with that from a solvent-based silicone TTS. FIG. 6b shows the cumulative 7-day permeation of **Rotigotine** rotigotine from a hot-melt silicone TTS through human skin.

[0021] FIG. 7 shows the cumulative **Rotigotine** rotigotine permeation, from hot-melt TTS with different hot-meltable cements, through murine skin.

[0022] FIG. 8 shows the cumulative permeation, through murine skin, of **Rotigotine** rotigotine from silicone-based hot-melt TTS produced in an extruder with different internal-phase components and a **Rotigotine** rotigotine content of 9%.

[0023] FIG. 9 shows the cumulative permeation, through murine skin, of **Rotigotine** rotigotine from EVA-based hot-melt TTS produced in the extruder with different **Rotigotine** rotigotine concentrations.

SUBSTITUTE SPECIFICATION (MARK-UP)

[0024] FIG. 10 illustrates an example of a TTS structure with an active substance-containing cement matrix (1), a backing (2) that is inert to the constituent components of the cement matrix, and a protective film (3) that must be removed before use.

[0025] **FIG. 11 is a diagram of a human-skin model used to determine rotigotine flux as described in Example 9.**

DESCRIPTION OF THE INVENTION

[0026] It was surprising to find that **Rotigotine** rotigotine lends itself superbly to processing by the hot-melt method, that it remains stable under short-term heating to temperatures up to at least 160°C[[]], that it can be homogeneously worked into matrices produced by the hot-melt process, and that it is released from the hot-melt matrices in continuous fashion and at a therapeutically desirable rate.

[0027] In particular, the inventors were surprised to find that the **Rotigotine** rotigotine, being susceptible to oxidation, remains stable in the hot-melt process even when heated to temperatures around 160°C. While at higher temperatures in an oxygen-containing atmosphere, **Rotigotine** rotigotine tends to decompose in oxidative fashion, it is amazingly stable in the hot adhesive melt and is present in the matrix at a purity level that is routinely better than 98% and generally over 99% (measured at 220 nm and 272 nm per HPLC; see tables 2, 3 and 4).

[0028] The preferred method is to introduce the **Rotigotine** rotigotine in its solid form into the homogenized matrix melt, *i.e.* the **Rotigotine** rotigotine is not melted until it is in the hot matrix. Following brief homogenization the **Rotigotine** rotigotine-containing cement matrix is cooled again so that, in general, the **Rotigotine** rotigotine is exposed to thermal stress for less than 5 minutes and preferably less than 4, 3 or even 1 minute(s). The **Rotigotine** rotigotine will then be present in the solidified melt. During that process the **Rotigotine** rotigotine is largely protected from critical environmental factors (light, oxygen).

[0029] The TTSs thus produced by the hot-melt method accept a high **Rotigotine** rotigotine charge of up to 40% by weight relative to the weight of the matrix.

[0030] Overall, the TTSs produced according to this invention by the hot-melt method offer a number of advantages over prior-art solvent-based TTSs:

- Since the **Rotigotine** rotigotine can be directly inserted in the adhesive melt, it eliminates the solvent-related problems when higher active-substance

SUBSTITUTE SPECIFICATION (MARK-UP)

concentrations are used. Consequently, substantially higher ~~Rotigotine~~ rotigotine concentrations (up to over 40 weight %) can be introduced in the TTS, in simple fashion, than would be possible in a solvent- and silicone-based process where ~~Rotigotine~~ rotigotine concentrations of more than about 15 weight % can no longer be worked in as a solution. It is thus possible to introduce surprisingly large ~~Rotigotine~~ rotigotine amounts even in relatively thin matrices, and in only one procedural step.

- The thickness of the layer can be varied over a wide range. For example, matrices having a weight of more than 100 g/m² and even more than 200 g/m² can be produced in a single step without difficulty. It follows that, in combination with the higher ~~Rotigotine~~ rotigotine concentration, a ~~Rotigotine~~ rotigotine content in the TTS matrix of up to 8 mg/cm² or even more is attainable. In contrast to that, it is not possible in a single-step operation to introduce a rotigotine charge of more than about 1.5 mg/cm² in a silicone TTS produced by the solvent-based process.
- The use, removal, recovery or disposal by incineration of organic solvents and the associated need for safety precautions in TTS production are eliminated.
- Hot-melt technology permits the continuous production of the TTS matrix from the weighing of its individual components all the way to lamination. That type of production cycle essentially offers the following advantages:
 - Processing times are substantially reduced.
 - The charge volume is determined via the operating time of the production facility. This avoids having to switch over to larger facilities with the associated scale-up problems and/or additional validation requirements.
- GMP-compliant production is possible using compact equipment with a small footprint.
- Using a suitable softener such as wax or the optional incorporation of an internal phase permits delayed release of the rotigotine from the cement matrix. An appropriate TTS configuration makes it possible to produce TTSs that release rotigotine over a span of several days, for instance 5, 6 or 7 days, in continuous fashion and therapeutically effective quantities.

[0031] Therefore, one object of this invention is a transdermal therapeutic system (TTS)

SUBSTITUTE SPECIFICATION (MARK-UP)

that encompasses a **Rotigotine rotigotine**-containing cement matrix, characterized in that the cement matrix contains a hot-melttable adhesive in which the active substance, **Rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]-amino]-1-naphthol) rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]-amino]-1-naphthol)**, is dispersed and partly or completely dissolved.

[0032] Another object of this invention is a TTS with a **Rotigotine rotigotine**-containing cement matrix produced by the hot-melt method employing a process in which the **Rotigotine rotigotine** is introduced, in molten or preferably in its solid form, into the 70-200°C[[.]] melt of the solvent-free cement matrix. The **Rotigotine rotigotine** is introduced in a solvent-free melt that is preferably heated to 100-170°C[[.]], desirably to 120-160°C[[.]] and ideally to 130-150°C[[.]], and then processed and cooled within 5 minutes, preferably within 3 minutes and ideally within a maximum of 1 minute after the admixture of the **Rotigotine rotigotine**.

[0033] The term “transdermal therapeutic system” refers to a pharmaceutical formulation or device that lends itself to the transdermal administration of an active substance through the skin of a mammal, especially through the human skin, in therapeutically effective quantities.

[0034] The term “hot-melt process” refers to a method that employs thermal energy for melting the hot-melttable adhesive and the optionally provided internal phase, thus obviating the need for solvents in the production of the cement matrix. By “hot-melt process” this patent application also subsumes a procedural variation involving work at temperatures below the melting point of **Rotigotine rotigotine**, whereby the adhesive melt contains the **Rotigotine rotigotine** in its solid form.

[0035] The term “solvent-free” as used in this patent application indicates that in producing the cement matrix no solvents are used that would have to be removed again in the course of the production process.

[0036] The term “hot-melttable adhesive” refers to an adhesive which, when applied to the skin, is pressure-sensitive and which can be processed by the hot-melt method at process temperatures of 70°C to 200°C[[.]], preferably 100°C[[.]] to 170°C[[.]], desirably 120°C[[.]] to 160°C[[.]] and ideally at temperatures between 130°C[[.]] and 150°C. The “hot-melttable adhesive” may consist of an adhesive or a mixture of different adhesives that are individually hot-melttable. Alternatively, the “hot-melttable adhesive” may be a mixture composed of an adhesive and a suitable softener.

SUBSTITUTE SPECIFICATION (MARK-UP)

[0037] These hot-melttable adhesives preferably have a dynamic viscosity which at 160°C[.] and especially at temperatures between 130°C[.] and 150°C[.] is at the most 150 Pa, preferably not more than 120 Pa, desirably less than 100 Pa and ideally less than 80 or even 60 Pa.

[0038] Examples of adhesives that are not hot-melttable *per se* include the commercially available silicone adhesives. At the aforementioned processing temperatures, silicone adhesives would be too viscous, having a dynamic viscosity of more than 150 Pa.

[0039] Existing patent literature discusses a variety of methods for making highly viscous silicone adhesives hot-melttable by admixing suitable additives (softeners). Examples of such softeners for silicones include glycerol monolaurate or lauryl acetate as described in EP 835 136, waxes along the formula R-C(O)-OR' as described in EP 360 467, alkylmethyl siloxane waxes as described in EP 524 775, siloxated polyether waxes as described in EP 663 431, or organic waxes as described in U.S. Patent No. RE 36,754.

[0040] The softeners are usually added to the silicone adhesive in quantities from 1-30 weight % relative to the overall hot-melttable cement mixture. The preferred softeners are organic waxes as described in U.S. Patent No. RE 36,754, such as ozokerite, ceresine, paraffin, candelilla, carnauba, bee's wax or mixtures of these waxes, with ozokerite and ceresine being particularly preferred.

[0041] Ready-mixed hot-melttable silicone adhesives, especially mixtures of silicone adhesives and ceresine or ozokerite, are available from Dow Corning in Michigan. Adding for instance 10 weight % of ceresine to a silicone adhesive succeeded in reducing the dynamic viscosity of the resulting adhesive mixture, at a processing temperature of 160°C[.], from over 150 Pa to below 50 Pa. That type of silicone-based adhesive mixture lends itself well to being processed by the hot-melt method within a temperature range from 100°C[.] to 200°C[.] and especially in the range between 120°C[.] and 160°C.

[0042] A surprising discovery showed that hot-melttable silicone adhesives are superbly suitable for the transdermal administration of **Rotigotine rotigotine**.

[0043] Therefore, one object of this invention is a transdermal therapeutic system (TTS) that encompasses a **Rotigotine rotigotine**-containing cement matrix, characterized in that the cement matrix contains a hot-melttable adhesive in which the active substance, **Rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol) rotigotine ((-)-**

SUBSTITUTE SPECIFICATION (MARK-UP)

5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]-amino]-1-naphthol, is dispersed and partly or completely dissolved, said hot-melttable adhesive containing a suitable mixture of a silicone-based adhesive and at least one softener.

[0044] Another aspect of this invention consists of a TTS that encompasses a cement matrix containing:

- (a) 50–99 weight % of an adhesive mixture composed of
 - (i) 70–99 weight % of an amine-resistant silicone adhesive and
 - (ii) 1–30 weight % of a suitable softener, and
- (b) 1–40 weight % **Rotigotine rotigotine**.

[0045] In a preferred implementation of the invention, the said silicone-based hot-melttable adhesive consists of

- (a) 70–99 weight % of an amine-resistant silicone adhesive and
- (b) 1–30 weight %, preferably 3–15 weight % and most desirably 4–10 weight % of an organic wax ideally selected from the group encompassing ozokerite, ceresine, paraffin, candelilla, carnauba, bee's wax or mixtures of these waxes, with particular preference given to ozokerite and especially ceresine.

[0046] As shown in FIG. 1a, a silicone-based hot-melt TTS of this simple composition produces *in-vitro* **Rotigotine rotigotine** permeation rates comparable to those of prior-art, therapeutically effective, solvent-based silicone TTSs.

[0047] FIG. 1b shows that, with an appropriately high infusion of the hot-melt silicone TTS per this invention, *in-vitro* flux rates can be achieved that are clearly above the rates attainable with prior-art, clinically effective, solvent-based silicone patches.

[0048] For the purpose of this patent application the term “hot-melt TTS” refers to a TTS whose cement matrix was produced by the hot-melt method, meaning by the solvent-free melting of the hot-melttable adhesive and, where applicable, additional components.

[0049] A surprising discovery showed that adding wax, especially organic wax such as ceresine or ozokerite, also has an effect on the *in-vitro* murine-skin permeation of **Rotigotine rotigotine** from the hot-melt silicone TTS. As is evident from FIG. 2, **Rotigotine's rotigotine's** permeation rate decreases as the wax concentration increases. This can be explained by a partial **Rotigotine rotigotine** distribution in the wax and a concomitant retardation effect.

SUBSTITUTE SPECIFICATION (MARK-UP)

[0050] This property of the wax is significant especially for developing a TTS designed for application over several days, for instance 7 days. That type of multi-day patch requires a high infusion of ~~Rotigotine~~ rotigotine, which poses the risk of an excessive release of ~~Rotigotine~~ rotigotine at the beginning of the application phase ("dose dumping"). It is therefore desirable to work into the TTS a component that controls the release of the active substance. This could be in the form of a membrane attached to the bottom of the matrix for controlling the release of the active substance. However, such a membrane increases material cost and makes the TTS structure more complex. It would therefore be desirable, instead of adding such a membrane, to include suitable retardant components in the matrix.

[0051] Apart from the surprising discovery that the wax content in the matrix serves to retard the release of the active substance, varying the wax content will not only modify the dynamic viscosity of the adhesive but additionally offers the equally surprising option of regulating the active-substance release.

[0052] As the wax content increases, the dynamic viscosity of the silicone adhesive initially drops off sharply to where the wax content is about 5 weight %, after which it decreases only slightly. Thus, when the wax content is 4-10 weight %, the dynamic viscosity of the silicone adhesive is at a level that suitably permits hot-melt processing while at the same time its effect on the ~~Rotigotine~~ rotigotine release is minor. Higher wax concentrations will additionally produce a retardation effect.

[0053] Similarly, the effect of the wax on the rheological properties of the TTS is surprising. If an organic wax is used as the softener for a silicone adhesive, the dynamic viscosity of the adhesive mixture decreases at elevated temperatures, which in excellent fashion permits the processing of the silicone-based cement mixture by the hot-melt method. At the same time, the rheological properties of the silicone, such as its cohesivity, unexpectedly remain fairly unaffected at room temperature, so that the typical problems with hot-meltable adhesives such as cold flux on the patient's skin are not encountered.

[0054] Suitable silicones include all of the silicone adhesives employed in adhesive-patch technology. The preferred silicone adhesives are amine-resistant, pressure-sensitive polyorganosiloxane adhesives.

[0055] In most cases, the silicone adhesives are polydimethyl siloxanes, but in principle it is just as possible to use in place of the methyl groups other organic radicals such as ethyl or

phenyl groups.

[0056] Amine-resistant silicone adhesives generally offer the advantage that they contain no or only few free silanol functions since their Si-OH groups were alkylated. That type of adhesives has been described in EP 180 377. The particularly preferred adhesive cements include condensates or mixtures of silicone resins and polyorganosiloxanes as described for instance in U.S. **Patent No.** RE 35,474.

[0057] These silicone adhesives are commercially available and are marketed for instance by Dow Corning as Bio-PSA Q7-4300 or Bio-PSA Q7-4200. Also available from Dow Corning are hot-melttable silicone adhesives that are mixtures of PSA 7-4300 with organic waxes such as ozokerite or ceresine.

[0058] The active substance, **Rotigotine rotigotine**, may be present at concentrations of 1 to more than 40 weight % relative to the weight of the total cement layer, either as a salt or in free-base form. Preferably, the cement matrix contains the **Rotigotine rotigotine** in free-base form.

[0059] Unlike the solvent-based silicone adhesives whose active-substance content is 15 weight % at the most, the adhesive matrices of hot-melt TTSs can accept significantly greater amounts of **Rotigotine rotigotine** without requiring any additional technical measures. That again provides greater flexibility in selecting the permeation rate and the release period of the hot-melt TTS.

[0060] As is evident from the example of a silicone-based hot-melt TTS in FIGS. 3a and 3b, a higher **Rotigotine rotigotine** charge allows for a higher flux rate through mammalian skin as well as a longer **Rotigotine rotigotine** release time. In applying a TTS on human skin, the particular effect of a higher **Rotigotine rotigotine** concentration is an extended **Rotigotine rotigotine** release while from an 8–9% **Rotigotine of rotigotine** concentration on up the permeation rate through human skin increases only marginally.

[0061] The preferred **Rotigotine rotigotine** concentrations in the adhesive layer are [[440]] **4–40** weight %, especially 9–30 weight % and more specifically 9–25 weight % or 15–25 weight %, for 7-day patches they are 20–40 weight % and especially 25–35 weight %, relative to the total weight of the adhesive layer.

[0062] Varying the layer thickness of the cement matrix serves as an additional element in controlling the **Rotigotine rotigotine** release rate and duration. The example of a hot-melt

SUBSTITUTE SPECIFICATION (MARK-UP)

silicone TTS in FIG. 4 shows the effect of the weight of the matrix on the *in-vitro* permeation of **Rotigotine rotigotine** through murine skin.

[0063] The thickness of the cement matrix can be flexibly selected over a wide range and in one single procedural step, since the layer thickness is not subject to the limitations associated with the solvent-based method. The layer thickness may be between 30 and 300 μm , preferably between 50 and 150 μm and most desirably between 50 and 120 μm .

[0064] The weight of the cement matrix of the TTS according to this invention is preferably between 30 and 300 g/m^2 , desirably between 50 and 150 g/m^2 and ideally between 50 and 120 g/m^2 ; for 7-day patches it is preferably 70–200 g/m^2 , desirably 80–180 g/m^2 and ideally 100–160 g/m^2 .

[0065] The preferred **Rotigotine rotigotine** content in the matrix is between 0.4 mg/cm^2 and 8 mg/cm^2 , depending on for how long the TTS is to be applied.

[0066] For a 1-day TTS the preferred concentration is between 0.4 and 1.5 mg/cm^2 and most desirably between 0.4 and 0.8 mg/cm^2 .

[0067] The average therapeutically required dose is about 6 mg of **Rotigotine rotigotine** per day. Hence, a 7-day patch requires about 42 mg of the active substance per TTS. For safety considerations, clinically employed transdermal systems are assumed to draw only about 50-60% of the TTS supply, which is why a 7-day TTS should contain at least 70 to 80 mg of the active substance.

[0068] Consequently, given a 7-day-patch TTS size of preferably 10–30 cm^2 and most desirably 15–25 cm^2 , the preferred **Rotigotine rotigotine** charge will be as follows:

Patch Size in cm^2	Minimum Rotigotine Content in mg/cm^2
10	7.0–8.4
15	4.7–5.6
20	3.5–4.2
25	2.8–3.4
30	2.3–2.8

[0069] Accordingly, the preferred **Rotigotine rotigotine** content in 7-day patches is between about 2 mg/cm^2 and 8 mg/cm^2 , desirably between about 2.8 mg/cm^2 and 5.6 mg/cm^2 and ideally between 3.1 and 5.6 mg/cm^2 .

[0070] So far, prior art has not disclosed any TTS for the administration of **Rotigotine**

SUBSTITUTE SPECIFICATION (MARK-UP)

rotigotine in therapeutically significant quantities at this high level, which at this point is possible only by the variable charging and layer thickness of the hot-melt TTS. The high Rotigotine rotigotine concentration of up to over 40 weight % makes it possible even for a 7-day TTS containing an appropriately large amount of Rotigotine rotigotine to produce relatively thin matrices with a layer thickness of 80–200 μm , preferably 80–180 μm and ideally 80–160 μm .

[0071] Another object of this invention therefore includes TTSs for the administration of Rotigotine rotigotine in therapeutically effective quantities, characterized in that they feature a Rotigotine rotigotine concentration in the cement matrix of at least 2.0 mg/cm^2 , preferably at least 2.8 mg/cm^2 and most desirably at least 3.1 mg/cm^2 or at least 3.4 mg/cm^2 . Preferred are TTSs containing matrices with a Rotigotine rotigotine change rate of over 20 weight % and a matrix weight of under 200 g/m^2 , for instance a weight of between 80 and 180 g/m^2 and most desirably between 80 and 160 g/m^2 .

[0072] As an option, the cement layer (also referred to as the cement matrix) may contain, in addition to the Rotigotine rotigotine and the adhesive mixture, a component that serves as the internal phase.

[0073] In particular, the internal-phase component serves as a solubilizer and crystallization inhibitor while contributing to a uniform distribution of the active substance in the cement matrix. The internal-phase component also helps augment moisture absorption of the patch on the skin.

[0074] For use in the hot-melt process, the most suitable internal-phase components are those exhibiting at temperatures below 170°C a dynamic melting viscosity of not more than 150 Pa, preferably less than 120 Pa and most desirably less than 80 Pa.

[0075] If at the desired processing temperature the dynamic viscosity of the internal-phase component is too low, a suitable softener such as glycerin may first have to be added. In some cases the active substance, Rotigotine rotigotine, may itself have softening properties. This is the case for instance with polyvinyl pyrrolidone so that, when PVP is to be metered into an extruder, a PVP/Rotigotine rotigotine premelt can be produced.

[0076] The internal-phase components are preferably selected out of the group of

- (a) hydrophilic or amphiphilic polymers,
- (b) hydrophilic or amphiphilic copolymers,

SUBSTITUTE SPECIFICATION (MARK-UP)

- (c) mixtures of (a) and/or (b) with pharmaceutically acceptable softeners,
- (d) condensates from glycerin with fatty acids or polyols, and
- (e) suitable mixtures of the substances (a)–(d).

[0077] Internal-phase components suitable for use in the TTS per this invention may be selected, for instance, from the group of polysaccharides, substituted polysaccharides, polyethylene oxides, polyvinyl acetates, polyvinyl pyrrolidones (PVP), PVPs with suitable softeners, polyethylene glycols, polypropylene glycols, acrylates, copolymers from polyvinyl pyrrolidone and (poly)vinyl acetate, copolymers from ethylene and vinyl acetate, as well as polyvinyl alcohols with a suitable softener such as glycerin.

[0078] The preferred internal-phase components are PVP, PVP with softener, polyethylene oxides (PEO), polyvinyl acetates (PVA), and copolymers from PVP and vinyl acetate.

[0079] The internal-phase component is added to the cement layer at a concentration of 0–40 weight % as related to the overall weight of the cement layer, with the preferred amount of the added internal-phase component being 2–25 weight %.

[0080] A surprising discovery was made whereby, given a constant amount of the active substance and perhaps a softener, the internal-phase component not only promotes the solubility of the **Rotigotine rotigotine** and thus its uniform distribution in the matrix but, as the quantity is increased, it also leads to a retardation, *i.e.* linearization, of the **Rotigotine rotigotine** release.

[0081] Using the example of a silicone-based hot-melt TTS, FIGS. 5a and 5b show the effect of the PVP content on the *in-vitro* **Rotigotine rotigotine** permeation through murine skin. As the PVP content is increased, it leads to a linearization of the **Rotigotine rotigotine** permeation rate (FIG. 5a) that is attributable to a significant reduction of the initial release of the active substance (FIG. 5b).

[0082] This retardation effect of the internal-phase component can be utilized for instance in the case of hot-melt TTSs with a high active-substance charge for producing a patch that releases the active substance, **Rotigotine rotigotine**, in uniform, therapeutically effective quantities over an extended period such as at least 3 days, or at least 4, 5, 6 or 7 days.

[0083] Assuming an average daily dose of 6 mg **Rotigotine rotigotine**, the necessary hourly steady-state **Rotigotine rotigotine** flux rate will be 250 µg. For a TTS with a surface

SUBSTITUTE SPECIFICATION (MARK-UP)

area of between 10 and 30 cm² that means a necessary flux rate of 8.3-25 µg/cm²/h.

[0084] In *in-vitro* permeation experiments on human skin with the disclosed silicone-based hot-melt TTS having a **Rotigotine rotigotine** charge of about 23–25 weight % and a patch weight of 54–84 g/m², *i.e.* a **Rotigotine rotigotine** content of 1.2–2.1 mg/cm² of matrix, it was possible to achieve continuous flux rates of 12–16 µg/cm²/h over a period of at least 3 days (see FIG. 6a).

[0085] That flux rate was on the order of magnitude of the clinically relevant flux rate obtained with the comparative silicone-based TTS produced by the solvent method. After about 48 hours, with the active-substance supply exhausted, the permeation curve of the comparative TTS broke off while the supply of the more highly charged hot-melt TTS was not exhausted even after 72 hours.

[0086] Applying the hot-melt TTS according to this invention on a human skin model as described in Implementation Example [[#]] 9, a **Rotigotine rotigotine** concentration of 25 weight % and a matrix weight of 85 µm² made it possible, after an initial lag phase, to maintain a 7-day steady-state flux rate through the human skin of about 15 µg/cm²/h (FIG. 6b).

[0087] Therefore, one object of this invention is a TTS whose cement matrix contains **Rotigotine rotigotine** as the active substance in an amount of at least 20 weight %, and preferably over 25 weight %, and which, in an *in-vitro* permeation test on human skin as described in Implementation Example [[#]] 9, leads to a continuous flux rate of at least 8 µg/cm²/h, or preferably 10 µg/cm²/h, lasting over a period of at least 5, 6 or 7 days.

[0088] Another object of this invention is a hot-melt TTS that contains **Rotigotine rotigotine** as the active substance in its adhesive layer in an amount of at least 20 weight % and preferably at least 25 weight % and which, in an *in-vitro* permeation test on human skin as described in Implementation Example [[#]] 9, attains a continuous flux rate of at least 8 µg/cm²/h for a period of at least 7 days.

[0089] For standardizing the solvent-based, **Rotigotine rotigotine**-containing silicone TTS, the *in-vitro* model per Tanojo (*J Contr. Release* 45 (1997) 41–47), used for measuring the flux rate through the human skin, has proved to be a good model for predicting the *in-vivo* flux rate determined in clinical studies. In contrast to a few other *in-vitro* human-skin models employed for comparison purposes, the flux rates through the human skin as determined by

SUBSTITUTE SPECIFICATION (MARK-UP)

the Tanojo model correlated excellently with the results obtained in clinical studies (Phase III) in terms of flux rates, plasma levels and clinical parameters such as the UPDRS score.

[0090] The results obtained with the model described in Implementation Example [[#]] 9 therefore suggest that the hot-melt TTS is equally suitable for the in-vivo administration of **Rotigotine** rotigotine in therapeutically effective amounts over a period of several days.

[0091] In clinical practice, the flux is preferably set at a rate where the patient maintains a continuous therapeutic plasma level of between 0.4 and 2 ng/mL of blood. This requires an hourly **Rotigotine** rotigotine flux through the patient's skin of 100–400 µg, preferably about 200–300 µg (corresponding to 10–15 µg/cm²/h for a 20 cm² TTS), desirably 230–270 µg and ideally about 250 µg. The standard dosage may be varied especially in adaptation to the patient's physical constitution. As shown in FIG. 6b, this flux rate is achievable over a 7-day period employing the TTS according to the invention.

[0092] Thus, for the first time, a TTS for the continuous transdermal administration of **Rotigotine** rotigotine is provided which, when applied on human skin, induces an average plasma concentration of 0.4–2 ng/ml **Rotigotine** rotigotine over a period of at least 5, 6 or 7 days.

[0093] Also for the first time, a TTS is provided that is capable of administering **Rotigotine** rotigotine through mammalian and especially human skin at an hourly flux rate of 200–300 µg over a period of 5, 6 or 7 days.

[0094] Therefore, one aspect of this invention is a TTS, preferably a hot-melt TTS and especially a silicone-based hot-melt TTS, that lends itself to the continuous administration of **Rotigotine** rotigotine over a period of at least 5, 6 or 7 days at a steady-state flux rate of 200–300 µg/day.

[0095] Another aspect of this invention is a TTS, preferably a hot-melt TTS and especially a silicone-based hot-melt TTS, that lends itself to the continuous administration of **Rotigotine** rotigotine to humans over a period of at least 5, 6 or 7 days, where over at least 80%, preferably at least 90% and most desirably at least 95% of the time selected the plasma level in the patient's circulatory system is set at between 0.4 and 2 ng **Rotigotine** rotigotine per mL of blood.

[0096] Another object of this patent application is a TTS for the transdermal administration of **Rotigotine** rotigotine, encompassing an active-substance-containing layer,

characterized in that:

- (a) the active-substance-containing layer
 - (a1) incorporates a **Rotigotine** rotigotine component of at least 20 weight % and preferably at least 25 weight %,
 - (a2) has a **Rotigotine** rotigotine concentration of at least 2.0 mg/cm², preferably 2.8 mg/cm² and most desirably at least 3.1 mg/cm² or at least 3.4 mg/cm², and
 - (a3) optionally contains an amount of an active-substance-retardant organic wax and/or an internal-phase component, and
- (b) upon application of the TTS on the patient's skin, will transcutaneously dispense **Rotigotine** rotigotine over a period of at least 5 days and preferably at least 7 days at a steady-state flux rate of 100–500 µg/hour and preferably 200–300 µg/hour.

[0097] Another object of the invention is a **Rotigotine** rotigotine-containing TTS, preferably a **Rotigotine** rotigotine-containing hot-melt TTS and, most desirably, a **Rotigotine** rotigotine-containing silicone-based hot-melt TTS, characterized in that:

- (a) the **Rotigotine** rotigotine is contained in the cement matrix in an amount of at least 20 weight % and preferably at least 25 weight %,
- (b) the cement matrix has a **Rotigotine** rotigotine content of at least 2.0 mg/cm², preferably 2.8 mg/cm² and most desirably at least 3.1 mg/cm² or at least 3.4 mg/cm², and
- (c) **Rotigotine** rotigotine is released to the patient over a period of at least 5, 6 or 7 days at a steady-state rate of at least 100–500 µg/hour, preferably 200–300 µg/hour and most desirably 230–270 µg/hour.

[0098] Those skilled in the art are familiar with other additives that may in principle be contained in the cement layer, such as antioxidants, stabilizers, tackifiers, preservatives or permeation boosters.

[0099] Whether the addition of such substances to the essential components per this invention, as defined in the claims, is useful in any given case can be determined by routine tests and such implementations are therefore specifically made a part of this invention.

[0100] In one preferred form of implementation of the invention the disclosed hot-melt TTSs do not contain any permeation boosters.

SUBSTITUTE SPECIFICATION (MARK-UP)

[0101] One form of implementation of the invention is therefore a hot-melt TTS encompassing a cement matrix that contains:

- (a) 50–99 weight % of a hot-melttable adhesive,
- (b) 1–40 weight %, preferably 5–30 weight %, desirably 9–30 weight % and ideally 15–25 weight % of **Rotigotine rotigotine**,
- (c) 0–40 weight %, preferably 2–25 weight % and most desirably 5–25 weight % of an internal-phase component preferably selected from among the group of polysaccharides, substituted polysaccharides, polyethylene oxides, polyvinyl acetates, polyvinyl pyrrolidones with or without softeners, polyethylene glycols, polypropylene glycols, acrylates, copolymers from polyvinyl pyrrolidone and **(poly)vinyl polyvinyl** acetate, copolymers from ethylene and vinyl acetate, as well as polyvinyl alcohols with a softener such as glycerin; **and**
- (d) 0–10 weight %, preferably 0–5 weight % and most desirably 0–3% of other additives such as tackifiers, antioxidants, stabilizers, **and** permeation boosters,

where the hot-melttable adhesive (a) is preferably a mixture of (i) 70–99 weight % of an amine-resistant silicone adhesive **and** (ii) 1–30 weight % of a suitable softener, especially a wax, preferably an organic wax and most desirably ozokerite or ceresine.

[0102] **Referring to FIG. 10, the** ~~[[The]]~~ hot-melt TTS may consist exclusively of the cement matrix, but in addition to the **Rotigotine rotigotine**-containing cement matrix it preferably includes such components as a backing (2) that is impermeable to the active substance and inert to the components of the cement matrix, and a protective foil (3) that covers the cement matrix (1) and must be removed before use (~~see FIG. 10~~). Those skilled in the art are familiar with other possible variations of the TTS configuration, including for instance an added membrane that controls the flux of the active substance, and/or an added adhesive foil (“overtape”). Particular preference is given to the “monolithic” TTS configuration depicted in FIG. 10.

[0103] Rotigotine is a dopamine agonist. Therefore, the TTS according to the invention is especially suitable for the treatment of diseases associated with dopamine-metabolic disorders, most particularly Parkinson’s disease or Restless Leg.

[0104] One object of the invention, therefore, is a method for treating dopamine-metabolic diseases, especially Parkinson’s disease or Restless Leg syndrome, characterized in

SUBSTITUTE SPECIFICATION (MARK-UP)

that a **Rotigotine rotigotine**-containing hot-melt TTS according to this invention is applied on the skin of a patient.

[0105] Another object of the invention is a product package holding one or several **Rotigotine rotigotine**-containing hot-melt TTSs per this invention as well as instructions for their use.

[0106] So far, the only methods known from prior art for the production of **Rotigotine rotigotine**-containing TTSs have employed a solvent-based **Rotigotine rotigotine**-containing cement matrix, requiring the removal of the solvent from a solvent-containing silicone- or acrylate-based dispersion. This present invention is the first to introduce a solvent-free hot-melt method for producing a **Rotigotine rotigotine**-containing TTS.

[0107] Therefore, one aspect of this invention is a method for producing a TTS encompassing a cement matrix that contains **Rotigotine rotigotine** as the active substance, characterized in that, prior to being laminated onto a foil, the components of the cement matrix are melted and homogenized, solvent-free, at temperatures of between 70 and 200°C[.], preferably between 100 and 200°C[.], and most desirably between 120 and 160°C. The ideal operating temperature in the extruder is between 130 and 150°C.

[0108] Surprisingly, it was found that, after the melting, the **Rotigotine rotigotine** remains stable in a variety of matrices even without the addition of stabilizers or antioxidants. HPLC measurements with UV analyses at 220 nm and 272 nm have shown that even without the admixture of antioxidants the purity level of the active substance routinely remained above 98% and generally better than 99% (**Table 24 Tables 2–4**; Implementation Examples [4, 6 and 7]).

[0109] Therefore, one aspect of the invention is the use of **Rotigotine rotigotine** in the production of a TTS, characterized in that the **Rotigotine rotigotine** is infused in the cement layer of the TTS by the hot-melt method.

[0110] It is entirely possible to introduce the **Rotigotine rotigotine** in the matrix either premelted or by metering it in solid form into the hot matrix melt where it is melted.

[0111] In a preferred form of implementation the **Rotigotine rotigotine** is melted at temperatures between 100 and 200°C[.], preferably between 120 and 160°C[.] and desirably between 130°C[.] and 150°C[.], in that **Rotigotine rotigotine** in its solid state is metered into the molten matrix, optionally without the addition of stabilizers or antioxidants.

SUBSTITUTE SPECIFICATION (MARK-UP)

[0112] In a particularly preferred form of implementation the **Rotigotine rotigotine** is melted by metering it, in its solid state, into the hot molten matrix and by briefly homogenizing and then calendering the **Rotigotine rotigotine**-containing matrix melt onto a foil substrate where it is cooled. In that operation the **Rotigotine rotigotine** is exposed, preferably for a maximum of 5 minutes and most desirably for less than 4, 3, 2 or even 1 minute(s), to a temperature of 100°C[.] to 200°C[.], preferably 120–160°C[.] and ideally 130–150°C.

[0113] Another aspect of this invention is, therefore, the use of **Rotigotine rotigotine** for producing a TTS by the hot-melt method at temperatures of between 120 and 160°C[.] and most preferably at 130°C[.] to 150°C[.], whereby the hot-melt process produces a cement matrix containing **Rotigotine rotigotine** at a purity level of at least 98% and preferably 99% as measured at 220 and 272 nm.

[0114] In another form of implementation of the invention, the cement layer of the TTS is melted at very low temperatures of 70–75°C[.], which is just below the melting point of **Rotigotine rotigotine**. That leaves the **Rotigotine rotigotine** in the matrix in its solid state. This method requires the use of hot-melttable adhesives that permit processing at 70°C[.], while on the other hand the dynamic viscosity of the adhesive mixture must not be set too low to avoid cold flux of the adhesive layer on the skin. The process therefore requires the application of a fairly high shearing force.

[0115] Therefore, one aspect of this invention is the production of a TTS by the hot-melt method, whereby the cement layer is melted at temperatures below the melting point of **Rotigotine rotigotine**, meaning below about 75°C[.], and the **Rotigotine rotigotine** in its solid state is metered into the melt.

[0116] For the industrial production of the TTS the cement layer is preferably prepared in an extruder. In that process, the individual components of the cement layer can be introduced in the extruder, for instance a dual-screw extruding machine, via the respective feed channels either separately or in premixed form. The combined substance is mixed in the extruder under controlled heating conditions, whereupon it can be continually processed and ultimately laminated.

[0117] Since at room temperature the hot-melttable adhesive remains solid, premelting is necessary. That can be accomplished for instance by means of a melting/metering system

SUBSTITUTE SPECIFICATION (MARK-UP)

consisting of a container with controlled heating, in which the hot-melttable adhesive such as the hot-melttable silicone adhesive is premelted at temperatures between 70°C[.] and 200°C[.], preferably between 100°C[.] and 170°C[.], desirably between 120°C[.] and 160°C[.] and ideally between 130 and 150°C. The melting/metering system permits continuous feeding, allowing it to be easily integrated into the continuous production system. The metering section may be of the volumetric or gravimetric type.

[0118] In hydrophobic adhesives such as silicones, **Rotigotine** rotigotine is soluble in trace amounts only, which is why it must be dispersed. The viscosity of the molten **Rotigotine** rotigotine is very low, as a result of which there may be considerable viscosity differences during the process between the adhesive and the active substance. For optimizing the distribution of the active substance in the cement matrix, one has the option of integrating static mixing agents in the extrusion process to ensure an even more homogeneous blending of the cement matrix. Suitable static mixing agents are available for instance from Sulzer Chemtech GmbH. It has thus been possible, as verified by microscope analyses of the cement matrix, to reduce the droplet size of the active-substance particles and of the internal-phase domains to an average of less than 20 µm.

[0119] There are several advantages to that:

[0120] For one, it prevents the formation of larger active-substance particles in the matrix that might lead to an uneven flux, to an adhesion/cohesion imbalance or to the recrystallization of the active substance.

[0121] For another, it prevents the accumulation of the active substance at the interface between the cement matrix and the skin that could cause skin irritation and/or protonation of the active substance with the consequent reduction of the flux rate through rediffusion of the protonized base.

[0122] Therefore, the size of the active microparticles should not exceed 80%, preferably 60% or ideally 50% of the thickness of the cement matrix. The average size of these microparticles is preferably in a range up to 40% and desirably up to 30% of the matrix thickness.

[0123] Assuming a matrix thickness for instance of 50 µm, the internal phase in the cement matrix would then preferably be in the form of droplets with an average size of up to 20 µm and preferably up to a maximum of 15 µm.

SUBSTITUTE SPECIFICATION (MARK-UP)

[0124] FIG. 8 shows the *in-vitro* permeation of ~~Rotigotine~~ rotigotine through murine skin from different silicone-based hot-melt TTSs produced by fused extrusion in an extruder under utilization of different internal-phase components.

[0125] Apart from the silicone-based adhesive systems, other hot-melttable adhesives are in principle equally suitable for use in the ~~Rotigotine~~ rotigotine-containing hot-melt TTSs according to this invention.

[0126] Hot-melttable adhesives have been described in prior art. Examples of usable types include hot-melttable adhesives based on styrene block copolymers ("SXS adhesives") derived from polymers with non-elastomeric styrene blocks at the ends and elastomer blocks in the middle. The elastomer blocks may consist for instance of polyethylene butyl, polyethylene propylene, polybutadiene or polyisopropene.

[0127] Adhesives of that type have been described for instance in U.S. Pat. No. 5,559,165 and U.S. Pat. No. 5,527,536. They offer good adhesive properties, are easy to produce and process and are well tolerated on the skin.

[0128] SXS adhesives can be procured commercially (*e.g.* as Duro Tak 378-3500 from National Starch & Chemical), or they can be produced using hot-melt extrusion equipment in the course of the production of the active-substance-containing patches. This involves the individual metering into and mixing and melting in the extruder of corresponding quantities (at least of the following components) of a styrene block copolymer (such as Shell Kraton GX1657 or Kraton D-1107CU) with a resin (such as Keyser-Mackay Regalite R1090 or Regalite R1010 or Regalite R1100) and an oil (such as Shell Ondina 933 or Ondina 941). As the last step, the active substance is metered into the adhesive thus produced in the extruder and the compound is then laminated onto a foil. Examples of typical polymer/resin/oil weight ratios are 100/120/20 or 100/200/50. By varying these ratios it is possible to adapt the properties of the SXS adhesive to the respectively desired properties of the TTS (adhesive strength, minimal cold flux, adhesive duration, release pattern of the active substance, *etc.*).

[0129] Because of the oxidative effect of the SXS adhesives a preferred method is to add antioxidants to such SXS-based cement matrices. One example of a commercially available, suitable antioxidant is Irganox® (by CIBA).

[0130] Another example consists in hot-melttable adhesives that are based on ethylene vinyl acetate copolymers ("EVA adhesives"). EVA adhesives of that type are described for

SUBSTITUTE SPECIFICATION (MARK-UP)

instance in U.S. Pat. No. 4,144,317. EVA adhesives offer good adhesive properties, they are easy to produce and process and are well tolerated on the skin. They are available for instance from Beardow Adams (13/BA).

[0131] It was possible both with hot-melttable SXS-type adhesives and with hot-melttable EVA-type adhesives to produce ~~Rotigotine~~ rotigotine-containing TTSs that encompassed hot-melt cement matrices and released the ~~Rotigotine~~ rotigotine in proper amounts (FIG. 7).

[0132] FIG. 9 shows the *in-vitro* permeation, through murine skin, of ~~Rotigotine~~ rotigotine from EVA-based hot-melt TTSs with varying ~~Rotigotine~~ rotigotine contents, produced by fused extrusion in an extruder.

[0133] Therefore, one object of this invention is a transdermal therapeutic system (TTS) encompassing a ~~Rotigotine~~ rotigotine-containing cement matrix, characterized in that the cement matrix contains a hot-melttable adhesive in which the active substance, ~~Rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]-amino]-1-naphthol)~~ rotigotine ((-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl)-amino]-1-naphthol], is dispersed and partly or completely dissolved, said hot-melttable adhesive being of the SXS-type or EVA-type.

[0134] One form of implementation of this invention is thus represented by a hot-melt TTS that comprises a cement matrix containing:

- (a) 50–99 weight % of a hot-melttable adhesive,
- (b) 1–40 weight %, preferably 5–30 weight %, desirably 9–30 weight % and ideally 15–25 weight % ~~Rotigotine~~ rotigotine, and
- (c) 0–40 weight %, preferably 2–25 weight % and desirably 5–25 weight % of an internal-phase component preferably selected from the group of polysaccharides, substituted polysaccharides, polyethylene oxides, polyvinyl acetates, polyvinyl pyrrolidones with or without softeners, polyethylene glycols, polypropylene glycols, acrylates, copolymers from polyvinyl pyrrolidone and (poly)vinyl acetate, copolymers from ethylene and vinyl acetate, as well as polyvinyl alcohols with a softener such as glycerin, plus 0–10 weight %, preferably 0–5% and most desirably 0–3% of other additives such as tackifiers, antioxidants, stabilizers and/or permeation boosters,

with the hot-melttable adhesive ~~per~~ (a) preferably selected as

- (a1) an EVA adhesive,
- (a2) an SXS adhesive, or
- (a3) a mixture consisting of
 - (i) 70–99 weight % of an amine-resistant silicone adhesive, **and**
 - (ii) 1–30 weight %, preferably 3–15 weight % and ideally 4–10 weight % of a suitable softener, preferably an organic wax – most desirably ceresine or ozokerite,

where, optionally, softeners may be added to the EVA adhesive (a1) and to the SXS adhesive (a2) and, if an SXS adhesive is used, an antioxidant is added.

[0135] If an individually hot-meltable adhesive for instance of the SXS type or of the EVA type is to be adapted to specific processing requirements, it is again possible, as an option, to add other substances to the composition, such as softeners, tackifiers, antioxidants, amphiphilic polymers, *etc.*

[0136] A comparison of the release pattern of **Rotigotine rotigotine** from the various hot-melt adhesives revealed that the TTS with the silicone-based hot-melt adhesive is the most efficacious. With the SXS-based and EVA-based hot-melt TTS, the **Rotigotine rotigotine** release drops off to a level that is no longer therapeutically effective at a point where about 30 weight % of the **Rotigotine rotigotine** is still present in the cement matrix. By contrast, the silicone-based hot-melt TTS allowed nearly total depletion.

[0137] Therefore, a **Rotigotine rotigotine**-containing hot-melt TTS produced with a silicone-based hot-melt adhesive as described above is given particular preference.

EXPERIMENTS: EXAMPLES

Comparative Reference Example: Solvent-based Silicone TTS

[0138] 1.8 g of (free-base) **Rotigotine rotigotine** was dissolved in 2.4 g ethanol and added to 0.4 g **Collidone Kollidon** 90 F (dissolved in 1 g ethanol). The resulting mixture was added to a 74% solution of silicone polymers (8.9 g **BioPSA BIO-PSA** 7-4201 + 8.9 g BIO-PSA 7-4301 [Dow Corning]) in heptane. After adding 2.65 g petroleum ether the mixture was agitated for 1 hour at 700 **[[RPM]] rpm** to produce a homogeneous dispersion. After lamination onto polyester it was dried at 50°C. The final weight of the patch was 50 g/cm².

[[1st]] **Example 1: Silicone-Based Hot-melt TTS with 15% Rotigotine Produced in Lab**

Quantities

(a) Silicone hot-melt adhesive

[0139] The silicone-based hot-melt cements employed contained the ~~BioPSA~~ **BIO-PSA** 7-4300 silicone adhesive (Dow Corning, Michigan) mixed with ozokerite or ceresine softeners at 5%, 10% or 15% of the overall weight of the adhesive mixture (purchased from Dow Corning).

(b) Producing the TTS

[0140] 8.5 g of a silicone-based adhesive mixture as described in (a) was heated to 160°C[[.]] over about 20 minutes until a homogeneous melt was obtained. 1.5 g (free-base) ~~Rotigotine~~ **rotigotine** was added and the mixture was kept at 160°C[[.]] for another 5 minutes. The mixture was then manually homogenized and laminated onto a preheated foil (120°C[[.]], gap width 250 µm). 5 cm² sections were then cut out.

[[2nd]] Example 2: Producing a Silicone-Based Hot-Melt TTS with an Internal Phase

[0141] This was produced as in Example [[#]] 1, with 0.5 g of an internal-phase component added together with the ~~Rotigotine~~ **rotigotine**.

[[3rd]] Example 3: Producing a Silicone-Based Hot-Melt TTS in Lab Quantities with Varied Parameters

[0142] The TTSs were in all cases produced as in Examples [[#]] 1 and [[#]] 2, while the different parameters such as the type of wax, the wax content, the concentration of the internal-phase component, the active-substance content and the patch density were varied as follows:

TABLE 1

<u>Silicone-based Hot-melt TTS</u>						
Lot No.	Ceresine Content [% w/w]	Ozokerite Content [% w/w]	Internal Phase Type & Content [% w/w]	Theoret. Rotigotine Content [% w/w]	Actual Rotigotine Content (n = 5) [% w/w]	Weight of Adhesive Matrix (n = 10) [g/m ²]
20011031	15	—	PVP/10	9	8.51	108
20011032	15	—	PVP/2	9	9.23	83
20011035	15	—	PVP/2	15	15.81	66
20011036	15	—	PVP/10	15	15.56	100
20012038	15	—	PVP/2	9	n.d.	123
20012040	15	—	PVP/2	15	n.d.	118
20012042	15	—	PVP/2	25	n.d.	114
20105042	15	—	0	15	15.25	57
20105043	15	—	PVP/25	15	14.04	127
20105038	15	—	0	9	8.75	91
20105039	15	—	PVP/2	9	9.07	88
20105040	15	—	PVP/10	9	9.14	91
20105041	5	—	0	9	8.08	106
20105043	—	5	0	9	8.03	105
20105044	15	—	0	15	14.50	78
20105045	15	—	0	25	25.20	77
20106016	—	15	0	9	8.12	88
20107040	—	5	0	15	13.71	99
20107041	—	5	0	25	24.71	84
20109009	—	15	0	15	13.28	89
20109010	5	—	0	15	14.09	107
20111059	—	5	0	25	23.95	54
20111058	—	5	0	15	14.57	54
20111057	—	5	0	9	8.64	56
20109043	—	5	0	25	22.69	117
20105044	—	15	0	15	14.49	57
20103043	—	15	0	15	14.04	78
WE11682*)	—	—	PVP/2	9	8.83	50
20107011*)	—	—	PVP/2	9	9.90	110

*)Solvent-based comparative reference example;

PVP = polyvinyl pyrrolidone

[0143] The **Rotigotine** rotigotine content and the weight of the cement matrix were determined as follows: 10 patches sized 5 cm², 10 cm² or 20 cm² were punched out and individually weighed, **and** the weight was corrected by subtracting the average weight of the blank foils (measured by weighing sections of the same size, *i.e.* 5, 10 or 20 cm², respectively).

[[4th]] Example 4: Producing SXS- or EVA-Based Hot-Melt TTS in Lab Quantities

[0144] 8.5 g of the SXS hot-melt adhesive (Duro-Tak 34-4230 by National Starch &

SUBSTITUTE SPECIFICATION (MARK-UP)

Chemical) or 8.5 g of the EVA hot-melt adhesive was heated at 160°C[.] for about 20 minutes until a homogeneous melt was obtained. 1.5 g or, respectively, 1.65 g of **Rotigotine rotigotine** base was added and the mixture was manually homogenized. The mixture was then laminated onto a preheated chill roll (120°C[.]). 5 cm² patches (for permeation experiments) and 20 cm² patches (for determining the patch weight) were then cut out. The matrix weight is shown in Table 2 below:

TABLE 2

Lot No.	Adhesive	Theoretical		Actual		Weight (n = 10) [g/m ²]	Purity % (220 nm/272 nm)
		Internal-Phase Content [% w/w]	Active-Substance Content [% w/w]	Active-Substance Content [% w/w]	Active-Substance Content [% w/w]		
20103041	SXS	—	15	14.96		85	94.9/94.3
20103048	EVA	—	16.2	18.24		58	98.1/99.7
20103047	EVA	—	16.2	15.96		127	98.8/99.9

[[5th]] Example 5: Producing a Silicone-Based Hot-Melt TTS with 15% Rotigotine and 5% Internal Phase in an Extruder

A. Producing a premelt of the silicone-adhesive mixture

[0145] The desired amount of the silicone-adhesive mixture as described in Example **[[#]]** 1 was preheated to 140°C[.] and placed in a metering unit (Meltex GR 12-1 by Melzer). The mixture was then volumetrically metered into the extruder.

B. Producing the cement matrix by the hot-melt method

[0146] A dual-screw extruder (25×24D by Dr. Collin GmbH) was used for small to moderate production quantities and a dual-screw extruder (ZSK25 by Werner Pfleiderer, Stuttgart) was used for large production quantities. The process conditions were 5 kg/h, with 120–140°C[.] heat zones. A Melzer CL200 was used for the laminating.

[[6th]] Example 6: Producing a Silicone-Based Hot-Melt TTS in the Extruder with Varied Parameters

[0147] The TTS was in all cases produced as described in Example **[[#]]** 5, with the parameters varied as follows:

TABLE 3

No.	Lot No.	Scale	Static Mixing	Ceresine Content [% w/w]	Internal Phase Type & Content [% w/w]	Theoret. Rotigotine Content [% w/w]	Actual Rotigotine Content (n = 5) [% w/w]	Matrix Weight (n = 10) [g/m ²]	Rotigotine Purity [%] (220 nm/272 nm)
1	20105025	large	—	15	PVA/10	9	8.88	117	99.3/99.7
2	20105025	large	+	15	PVA/10	9	7.16 ^{a)}	117	99.3/99.9
3	20105018	large	—	15	PVA/10	9	9.16	92	99.4/100
4	20105018	large	+	15	PVA/10	9	8.36	86	99.5/100
5	20109006	small	—	15	PVA/10	9	8.80	82	99.6
6	20109007	small	—	15	PVPVA/10	9	8.96	98	98.3
7	20109008	small	—	15	PEO/10	9	7.28	88	99.1
8	20108030	small	+	15	—	25	22.43	187	99.2/n.d.
9	20105045	small	—	15	—	25	25.2	77	98.7/96.9

PVA = polyvinyl acetate;

PEO = polyethylene oxide

PVPVA = polyvinyl pyrrolidone-vinyl acetate copolymer

[[7th]] Example 7: Producing EVA-Based Hot-Melt TTS in an Extruder

[0148] All TTSs were produced as described in Example [[#]] 5, with the TTSs having the following compositions:

TABLE 4

Lot No.	Scale	Internal-Phase Content [% w/w]	Theoretical Active-Substance Content [% w/w]	Actual Active-Substance Content (n = 5) [% w/w]	Weight (n = 10) [g/m ²]	Rotigotine Purity [%] (220 nm/272 nm)
20103048	small	—	16.2	18.24	58	98.1/99.7
20103047	small	—	16.2	15.96	127	98.8/99.9
20109019	large	—	9	8.62	93	98.9/99.9
20109045	large	—	15	15.08	104	99.4/n.d.
20109020	large	—	20	18.57	89	96.1/n.d.

[[8th]] Example 8: Determining the Flux of the Active Substance in the Murine-Skin Model

[0149] For measuring the flux through murine skin, abdominal and dorsal skin about 120 to 150 μ m thick was used. A punched-out TTS with a surface area of 2.55 cm² in a horizontal diffusion cell was fastened to the keratic side of the abdominal and dorsal skin of hairless mice. Immediately thereafter the acceptor chamber of the cell was filled with a phosphate buffer solution (0.066 molar) preheated to 32°C[[.]], with a pH 6.2 and bubble-free, and the release medium was thermostatically controlled at 32 \pm 0.5°C.

[0150] At the time of the sampling the release medium was replaced with fresh medium thermostatically controlled at 32 \pm 0.5°C. The ~~Rotigotine~~ rotigotine release was determined

SUBSTITUTE SPECIFICATION (MARK-UP)

by HPLC as described in Example [[#]] 10.

[[9th]] Example 9: Determining the Rotigotine Flux in the Human-Skin Model

[0151] The Rotigotine flux through human skin was essentially determined as described by H. Tanojo *et al.* in J. Control Rel. 45 (1997) 41–47.

[0152] For that purpose, human skin about 250 μm thick was harvested from an abdomen. A TTS with a surface area of 2.545 cm^2 was applied on an identical area of the human skin, with the skin on the acceptor side resting on a silicone membrane (~~diagram-1~~ **FIG. 11**). The acceptor phase used was PBS (0.066 molar) at pH 6.2 and a temperature of $32 \pm 0.5^\circ\text{C}$. The experiments were conducted with a flux of 5 mL/h over 72 hours, with samples taken every 3 hours. At the time of the sampling the release medium was replaced with fresh medium thermostatically controlled at $32 \pm 0.5^\circ\text{C}$ [[.]] and the amount of the released **Rotigotine** rotigotine was measured by HPLC. The flux rate $Q(t)$ relative to the surface of the measuring cell (0.552 cm^2) was determined using this formula:

$$Q(t) = \mu\text{g}/\text{cm}^2 = \text{Rotigotine } \underline{\text{rotigotine}} \text{ concentration acceptor volume divided by } 0.552 \text{ cm}^2$$

[[10th]] Example 10: Rotigotine Analytics

(a) Analytics of the active-substance release

[0153] The flux of the active substance through the skin preparations was measured by HPLC (RPC18 LichroCART 75-4 Supersphere 60 select column) under the following conditions: 650 parts by volume (VP) water, 350 VP acetonitrile, 0.5 VP methane sulfonic acid; room temperature; wavelength: 272 nm; flux 2 mL.

(b) Analytics of the active substance in the matrix

(b1) Preparing the matrix

[0154] The cement matrix was mixed with 0.1% methane sulfonic acid, agitated, centrifuged and measured.

(b2) Analytics of the active-substance content

[0155] The active-substance content was determined by isocratic HPLC under the following conditions:

Solubilizer: 65 volume parts water with 0.05% methane sulfonic acid; 35 volume parts acetonitrile with 0.05% methane sulfonic acid.

SUBSTITUTE SPECIFICATION (MARK-UP)

Column: LiChroCART 75×4 mm, Supersphere 60 RP-select B 5 µm.

Flow rate: 2 mL/min, column temperature: 30°C.

UV detection (272 nm).

(b3) Analytics of the active-substance stability:

[0156] The purity of ~~Rotigotine~~ rotigotine was determined by the gradient HPLC method with an aqueous and an organic (acetonitrile) phase, each with 0.05% methane sulfonic acid added. The organic component rose from the initial 5% to 60% over 35 minutes.

Column: LiChrosphere 100 CN, 125 mm × 4.6 mm, 5 µm.

Flow rate: 1.0 mL, column temperature: 40°C.

UV detection (2 wavelengths[~~[,]]~~: 272 and 220 nm).

(b4) Determining the dynamic viscosity

[0157] The dynamic viscosity was determined as described in U.S. Patent RE 36,754.